REMARKS

Claims

Claims 40–59 and 63–68 are pending. Claims 1–39 and 60–62 were previously cancelled without prejudice or disclaimer.

Claims 50, 58 and 63–68 are directed to the elected subject matter pursuant to the restriction response mailed June 22, 2010 and Applicants' response thereto filed November 22, 2010.

Claims 40-49, 51-57, and 59 are withdrawn from consideration because they are alleged to be directed to non-elected subject matter.

Claims 68–70 are added by this paper.

Claim amendments

The claims are directed to the treatment of diabetes or obesity using human pleiotrophin polypeptides of the instant application, including functional fragments thereof (or compositions comprising such polypeptides or their fragments). Applicants' amendment of the claims is not to be construed as acquiescence to any ground of rejection set forth in the Office Action.

Claim 63 has been recast as an independent claim.

Support for the amendment to claim 66 can be found in, for example, paragraphs [0064-0068] of the published US specification (US application pub. No. 20100162421).

The amendment of claim 66 is supported by, for example, the disclosure in paragraph [0064] of the published specification.

Support for the new claim 68 can be found in, for example, paragraph [0022] of the published US specification. New claim 69 is supported by the disclosure in, for example, paragraph [0042] of the specification.

The subject matter cancelled from claim 65 is now presented in new claim 70.

It is respectfully submitted that the amendments do not recite new matter. Entry thereof is respectfully requested.

Abstract

Applicants request entry of the ABSTRACT after the claims section of the instant application in a new sheet of paper. The abstract is identical to that which appears on

the cover page of the international application PCT/EP2004/007917 (of which the instant application is a US national stage entry under §371). No new matter is added.

Rejections under 35 U.S.C. §112, ¶2 (indefiniteness)

Claim 65 is allegedly indefinite in reciting that the diabetes is insulin-dependent diabetes mellitus or non-insulin-dependent diabetes mellitus. According to the Examiner the wording implies that there are other types of diabetes. This contention and the rejection based thereon are both without merit. A skilled worker understands that diabetes as recited generally in claim 58 includes both mellitus and insipidus forms, whereas claim 65 differentiates between sub-types of diabetes mellitus. In any event, the foregoing amendments render the rejection moot. Withdrawal of the rejections is respectfully requested.

Rejection under 35 U.S.C. §112, ¶4 (improper dependency)

The amendment of claim 63 renders the rejection moot. Withdrawal of the rejections is respectfully requested.

Rejection under 35 U.S.C. §112, ¶1 (Written description)

At page 3 of the Office Action, it is alleged that "Claims 50 and 58 are not original claims and these claims have been substantively amended. No basis has been pointed to in support of these claims and none is apparent." This contention is respectfully traversed.

Claim 50 is directed to methods for the treatment of diabetes or obesity, comprising administering to a subject in need thereof, a human pleiotrophin polypeptide or a functional fragment thereof. Claim 58 is directed to methods for the treatment of diabetes or obesity, comprising administering to the subject in need thereof a medicament comprising an acceptable carrier and a human pleiotrophin polypeptide or a functional fragment thereof. Original claims 50 and 58, which recite these embodiments in use claim format, provide adequate basis for these claims. Accordingly, the Examiner's contentions regarding alleged lack of written description for the treatment of metabolic diseases or metabolic dysfunction (see page 3 of the Office Action) is thus moot. Applicants' amendment of the claims is not to be construed with acquiescence to

this or any other grounds of rejection set forth in the Office Action.

Written description of the biomolecules of the instant application and use thereof

With respect to the recited isoforms, fragments or variants of SEQ ID NO: 2, the Examiner alleges that there is no support for the use of pleiotrophin variants recited in (d), (e) or (f) of claim 63 for the treatment of diabetes. This contention is misplaced. The descriptive portion of the instant specification, for example, the paragraphs bridging page 7, lines 35 to page 8, line 16, explicitly teaches to those skilled in the art that the claimed pleiotrophin variants are useful for the treatment of diabetes and/or obesity, as claimed. To this end, paragraph [0034] of the published specification expressly teaches that "DG001 (or pleiotrophin) is a strong candidate for the manufacture of a pharmaceutical composition and a medicament for the treatment of conditions related to human metabolism, such as diabetes, obesity, and/or metabolic syndrome."

With respect to diabetes and obesity, the specification, for example, paragraph [0029] explicitly teaches that "DG001 is strongly down-regulated in metabolic active tissue (WAT) which [supports] an essential role of DG001 in the regulation of the mammalian metabolism, particularly in processes related to, obesity, diabetes, or metabolic syndrome." Paragraph [0035] further teaches that "DG001 induces the differentiation of insulin-producing cells and is thus a target for the treatment of diabetes."

With respect to the genus of pleiotrophin molecules, the specification teaches that "DG001 homologous proteins and nucleic acid molecules coding therefor are obtainable from vertebrate species. Particularly preferred are nucleic acids encoding the human DG001 protein and variants thereof. The invention particularly relates to a nucleic acid molecule encoding a polypeptide contributing to regulating the energy homeostasis and the mammalian metabolism, wherein said nucleic acid molecule comprises the nucleotide sequence of human DG001 (SEQ ID NO: 1) which encodes human DG001 protein (SEQ ID NO: 2)." Variants of human pleiotrophin polypeptide are further described in paragraph [0022] of the published specification.

With respect to the fragments, the specification at paragraph [0042] explicitly teaches that "the invention relates to peptide fragments of the proteins…having a length of at least 4, preferably at least 6 and up to 50 amino acids." Thus the disclosure

in the original specification conveys to those skilled in the art that Applicants were in possession of the claimed embodiment of the present invention on or before the filing date of the instant application.

In any event, claims 68 and 69 are free from the Examiner's insufficient rationale.

Regarding claims 66 and 67, the Office Action alleges that there is no disclosure of contacting any cell that expresses any pancreatic gene. Again, this contention is misplaced. The Examiner's attention is directed to the disclosure on page 37, lines 10-18 of the original specification, wherein it is clearly stated that the cells expressing a variety of pancreatic genes but not limited to Pax-4 can be contacted with media containing the pleiotrophin polypeptide and differentiated. As such, contrary to the Examiner's contentions, the disclosure in the specification literally discloses the claimed pleiotrophin polypeptides of the instant application and uses thereof in the treatment of diabetes and/or obesity.

Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, ¶1 (enablement)

The Examiner contends that claims 50, 58 and 63-67 fail to comply with the enablement requirement allegedly because of the breadth of the genus of pleiotrophin polypeptides, types of disorders/diseases that can be treated, and the setting in which the embodiments are to be practiced. Applicants request reconsideration of the rejection in view of the amendment of the claims to delete isoforms and variants of the claimed polypeptides. No acquiescence to any of the contentions raised in the Office Action is to be implied. Applicants further submit that in view of the arguments submitted with the Reply of May 24, 2010, the original specification enables those skilled in the art to make and use the claimed genus of pleiotrophin proteins in a manner recited in the claims.

Claims 68 and 69 are directed to use of pleiotrophin proteins having a high degree of sequence identity to the wild-type pleiotrophin protein of SEQ ID NO: 2 and/or functional fragments thereof. In view of the decision in *Ex parte* Kubin, Appeal No. 2007-0819, B.A.P.I. 2007 and Applicants' remarks spanning pages 14 and 15 of the previous reply, it is submitted that the rejection should be withdrawn. The claims are

further directed to "functional fragments" of the claimed pleiotrophins, which is a term understood by those skilled in the art as fragments that substantially retain the biological function of the parent peptide. Representative examples of such fragments are known in the art. To this end, the post-filed article by Duces et al. (*Molecular Cancer Therapeutics*, 7, 2817, 2008) teaches that a 16-kDa fragment of pleiotrophin acts on endothelial and breast tumor cells to inhibit tumor development. Preferred types of functional fragments, for example, having the structural characteristics recited in new claim 69, are further disclosed. Favorable action is earnestly solicited.

Alleged lack of enablement with respect to the use of pleiotrophin polypeptides

Applicants respectfully traverse the Examiner's contention at page 4 of the Office Action, wherein it is alleged:

> The specification does not disclose nor exemplify administering DG001 polypeptide or a functional fragment thereof to treat any disease or condition embraced by the claims. No regeneration of any pancreatic cells or tissues is exemplified. No modulation of pancreatic development in a subject is exemplified. No production of insulin producing β cells from any cell or any pluripotent stem cell is exemplified.

This contention lacks scientific merit. The disclosure in the Examples section of the specification explicitly conveys that pleiotrophin induces the differentiation of embryonic stem cells into insulin-producing cells and further such differentiated cells respond to glucose in a manner that is similar to β-cells. As for explicit recitation of the use of such cells for therapeutic end uses, it is not necessary to state each and every step in detail as required by the Examiner. Controlling case law has unequivocally held that the provision of *in vivo* experimental evidence is not a requirement for patentability of claims to therapeutic compositions nor methods of treatment. See *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985) and pages 12–13 of Applicants' remarks filed May 24, 2011. The original specification clearly conveys that insulin-producing cells were in fact generated *ex vivo* and that *in vivo* transplantation of such cells into diabetic mice can be an effective strategy to relieve hyperglycemia associated with diabetes.

Although not required because the original disclosure is enabling, enclosed herewith for the Examiner's consideration are experimental data which

demonstrate the effect of pleiotrophin proteins. In these studies, the damage of the endocrine pancreas as a result of diabetes or obesity was mimicked by inducing apoptosis of rat insulinoma β-cell-line (INS-1E cells) with cytokines (interferon-γ and interleukin-1β). Simultaneous treatment with DG001 protein significantly reduced β-cell apoptosis in a dose-dependent manner (see Fig. 1). Moreover, the results show that treatment with the DG001 protein leads to a significant increase in beta cell proliferation in a dose-dependent manner (see Fig. 2). Reconsideration of the rejection in view of the enclosed Exhibit A is respectfully requested.

Should the Examiner find the data in the Exhibit useful, Applicants will be happy to file the enclosed data in the form of a declaration under CFR §1.132.

In view of the aforementioned amendments and remarks, it is respectfully submitted that Applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with an effort that is routine with in the art.

Withdrawal of the rejection under 35 U.S.C. §112, ¶1, is respectfully requested.

Rejections under §102(e)

Claims 50 and 58 are rejected under 35 USC §102(e) as allegedly anticipated by Colley et al. (US patent app. pub. No. 2003-0202960; hereinafter "the '960 publication"). This contention is respectfully traversed.

Colley's disclosure in the '960 publication is directed to the use of pleiotrophins for stimulating angiogenesis in a human or animal in need thereof. In the paragraphs spanning [0011], [0014] and [0015] of the '960 publication, Colley teaches using pleiotrophin for treating cardiovascular diseases, coronary artery diseases, ischemic heart diseases, vasculopathies, peripheral atherosclerotic diseases, osteoporosis or arthritis. Colley is silent on the use of pleiotrophin proteins in the treatment of diabetes or obesity as recited in the present claims.

With respect to treatment of diabetes, it should be noted that the cited reference only teaches treatment of wounds associated with diabetes. Thus, in paragraph [0037], Colley teaches that wounds associated with diabetes (such as diabetic ulcers) or those occurring in immunosuppressed or immunocompromised patients may be treated, for

example, in patients undergoing cancer chemotherapy, patients with acquired immunodeficiency syndrome (AIDS), transplant patients, and any patients suffering from medication-induced impaired wound healing. Such a teaching, even at its broadest interpretation, is not equivalent to treatment of diabetes, as recited in the present claims.

With respect to the PTO's contention that the preamble of the instant claims reciting treatment of diabetes or obesity by performing the claimed method steps is not limiting, the Examiner's attention is directed to the administrative guidelines which buttress MPEP §2111.02. Therein it is explicitly stated that "a 'preamble may provide context for claim construction, particularly, where that preamble's statement of intended use forms the basis for distinguishing the prior art in the patent's prosecution history.'" Thus the preamble of the instant claims should be given patentable weight. See Metabolite Labs., Inc. v. Corp. of Am. Holdings, 370 F.3d 1354, 71 USPQ2d 1081 (Fed. Cir. 2004) and Catalina Mktg. Int'l v. Coolsavings.com, Inc., 289 F.3d 801, 62 USPQ2d 1781 (Fed. Cir. 2002). The court in *Catalina* held that "clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention." Reconsideration of the instant claims in accordance with this guidance is respectfully requested.

In reconsidering the pending rejection, the Examiner is requested to review the administrative guidelines under MPEP §2131, which states that to support a rejection under §102, "the identical invention must be shown in as complete detail as is contained in the ... claim." See also *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 9 USPQ2d 1913 (Fed. Cir. 1989). Without such, the holding of anticipation cannot stand. Accordingly, Colley fails to anticipate the claimed invention. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above remarks, favorable reconsideration of the pending rejections is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

Applicants' remarks filed with the Reply of May 24, 2011 are incorporated by reference herein in their entirety.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

/Sagun KC/

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Sagun KC, Reg. No. L0510
For Applicant(s)

/Diana Hamlet-Cox/

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Diana Hamlet-Cox, Reg. No. 33,302
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

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